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Dr. Victor A. McKusick
Chairman
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Dear Vic,

I append a run-down of a proposed schedule for the Wednesday morning, first week, Bar Harbor session.

1. Introduction by Boyer. Intent of morning to be outlined, namely, use hemoglobin as frame of reference as a model system for understanding at a molecular level what genes are and what they do. The keynote will be structure function, whether it be structure of DNA and its function or structure of a protein and its function. We'll depend on the fact that this is a course in medical genetics and emphasize the role of structure function operations as they cause disease, or as they enable people to understand some of the later stuff.

In the introduction I'll tell them what proteins are, what hemoglobin is, the kinds of hemoglobin, the fact that it's under the control of a multiplicity of genes and then I will take each of the keynote ideas which the subsequent speakers will utilize. I'll be aided by a handout of references put together from the contributions of all speakers and further by a glossary which will define the terms which we use. I'll also be aided by a handout which summarizes by figure various features of hemoglobins including a list of mutants, a list of sequences and some notion of tertiary structure. My introduction will last approximately 15 minutes.

2. Roberto Poljak will do Howard Dintzis' thing on structure function. Specifically he will show ways in which the quaternary organization of the molecule lends itself to hemoglobin function and have reference to mutants as he needs them. His remarks will consume about 30-40 minutes. You should note that in each of the sessions we allow time for questions in the intervals indicated. That is, the 40 minutes just referred to includes questions.

3. The nature and effects of mutations. Here I'll come back on and spend 40 minutes giving generally the kind of talk that I give to the medical students with strong emphasis on the kinds of mutations that exist, that is single and multiple nucleotide changes. I'll refer to mutation rate, the frequency of mutants and will lean on the notion of genetic heterogeneity. I'll deal with the problems not only of point mutations but of the non-point multinucleotide changes that result in deletions, additions, new loci, etc.

Hopefully, this will get us up to coffee break which, on that day if at all possible, should come a little early, say about 10:05 or 10:10.

4. After a 30 minute coffee break Kirby Smith will run us back to the gene and discuss genomic organization. He'll introduce the conceptions of repeated DNA vs. unique DNA and lean on the notion that we can't know very much about genetics until we learn something about the function of the vast quantity of repeated DNA which represents something approaching 70-90% of the entire genomic content. In order to deal with this he will necessarily have to deal with transcription and the various kinds of RNA that result, that is ribosomal RNA, transfer RNA, heterogeneous nuclear RNA, and messenger RNA. He knows very well that this is a course in medical genetics and not in molecular biology and intends to tie each of these notions to human problems. Kirby will consume approximately 40 minutes in this discussion.

5. Haig Kazazian will then come on and follow up with the rudiments of translation simply setting them out as opportunities for mutation. He will again describe these rudiments of translation, the translational elements in terms of the hemoglobins. He will then focus on all of the kinds of information which we have developed in terms of thalassemia. Haig is going to need about 40 minutes to do this job.

6. At the end, having gone from structure and function in the proteins and gone from structure and function of DNA-RNA we have ended up at "physiological genetics". I then would like to have Tibby come on for a period of 20-25-30 minutes and develop aspects of the mouse models as they are problems of the integrated whole.

In all of the foregoing I have left out much detail. I haven't said that I'll be doing structure and function with a selected set of mutants building on what Roberto has said. I haven't said that Haig, after he has done translation, will return to the differentiation and organization of hemoglobins in maturation, that he will go to the cellular level before he gets to thalassemia. We don't intend to clutter up the stage with innumerable examples, but rather hope to lean on a set of concepts with particular examples. Our concepts will be stated in an outline which we will hand out.

I recognize that in terse form such as this, it can all sound rather vague and wooly. You may have this feeling particularly about the stuff that

Boyer - 20
Poljak - 40
Boyer - 40
to 10:10

10:40 - 11:20
11:20 - 12:00
12:00 - 12:30 Tibby

Kirby is going to do, namely genomic organization. My feeling is that this is terribly important and gives us a look at the next generation of problems and further gives us a look at where, I believe, most of the great advances with regard to differentiation, regulation, and all that are going to come from. In short, I propose to give them a lot of information, but at the same time give them a look at the directions ahead.

I've told all parties that we'll have to have a detailed working outline including our glossary and references by the afternoon of July 3. It should be then possible to work that over and get it to you by July 10. I won't contact Tibby until I've heard your reaction to all of this.

Although we've talked it over I am making only this one copy to send to you and not circulating this memorandum to the other speakers at the moment.

I don't plan to do the "geographic and racial distribution of inherited diseases" in my talk on evolution. As I understand it, you and I are sharing that evening at about a 50-50 split. I suppose that means that we will each have about an hour which is a 50 minute talk allowing time for questions. That evening I shall not have much more time than to first define terms, introduce evolution as simply an extention of the structure function concept illustrated in a few ways, and then opt for selection as the primary architect of change. In this I will have something to say about the problem of Darwinian vs. non-Darwinian evolution if only because that is a topic they may have heard about and will cause confusion. I'll come down firmly on the notion of Darwinian evolution as responsible for the polymorphisms. Since it's an evening talk I'll sort of work in the social notions as well and I'll have necessarily, therefore, recourse to some of the "geographical and racial" aspects. Here I think I'll stick to sickle and lactase.

I always have the feeling in this course that you've got to give both facts and basic concepts on the one hand, and on the other show them where the edge of information, understanding and viewpoint lies.

Sincerely,

Samuel H. Boyer, M.D.
Professor of Medicine

SHB:jbg